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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/801,196	WANG ET AL.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-7 and 25-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-7 and 25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet.*

Continuation of Attachment(s) 6). Other: abstracts for Bodey et al and Kerkela et al.

DETAILED ACTION

1. Currently, claims 1, 3-7 and newly added claims 25-31 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are newly applied, necessitated by amendment. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

3. Claims 1, 3-7 and 25-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to nucleic acids that consist of SEQ ID NO 1 or comprise a nucleotide sequence "as set forth in SEQ ID NOS 3, and 5", sequences having at least 85% identity to the nucleotide sequence set forth in SEQ ID NO: 5, complements

of SEQ ID NOS 1, 3, and 5, nucleic acids that encode and MMP-25 polypeptide variant which comprises an amino acid sequence at least 90% or 95% identical to SEQ ID NO 6, vectors and host cells comprising such sequences as well as method of detecting a nucleic acid encoding all or part of MMP-25 by detecting hybridization with oligonucleotides encoding a peptide consisting of amino acids 1-61, 98-111 or 161-170 of SEQ ID NO: 6. Such recitation encompasses mutants, variants, and homologs of SEQ ID NOS 1, 3, and 5, from any source. However, the specification does not provide enough guidance to the skilled artisan to make or use sequences commensurate in scope with the broadly claimed invention.

The specification teaches that SEQ ID NO 5 encodes a matrix metalloprotease that has the highest % identity to the stromelysin family of matrix metalloproteases (46%). The specification teaches that SEQ ID NO 3 encodes a splice variant of SEQ ID NO 5,which lacks a Zn binding domain. The specification teaches that SEQ ID NO 1 encodes a fragment of SEQ ID NO 5, and SEQ ID NO 3. The specification teaches that the claims encompass variants that retain structural and functional characteristics more similar to MMP 25 (polypeptide encoded by SEQ ID NO 5) than to non type MMP 25 polypeptides. However, the specification does not teach the specific biological activity or function of SEQ ID NOS 3 or 5, such that the skilled artisan could predictably determine whether a nucleic acid encoded a matrix metalloprotease or MMP 25, based solely on it's nucleic acid sequence or it's ability to hybridize to parts of SEQ ID NO 5.

While SEQ ID NO 5 appears to belong to the family of Matrix Metalloproteases, Matrix Metalloproteases comprise a large group of proteins that are involved in the degradation of the extracellular matrix (see Yang and Kurkinen, J. BC, 1998; vol. 273, p

17893, col 1). This large group of proteins share similar domains with distinct structure and function, and have wide and often overlapping substrate specificities depending on the group they are in. These groups include collagenases, gelatinases, stromelysins, and membrane-type MMPs. However, this large group of proteins have different biological functions. Nagase teaches (Nagase and Woessner, J. BC, vol. 274, pp 21491-21494; 1999) that MMPs participate in many normal biological processes such as embryonic development, organ morphogenesis, nerve growth, apoptosis, etc (see p. 21493, col. 1 "Biological and Pathological Roles of Matrixins"). Nagase teaches that while the main function of matrixins is removal of the extracellular matrix during tissue resorption and progression of many diseases, MMPs also alter biological functions of extracellular matrix macromolecules by specific proteolysis. Nagase teaches that MMP-2 cleaves the Ala586-Leu587 bond in laminin and induces the migration of normal breast epithelial cells. In contrast, cleavage of type I collagen by MMP-1 and MMP-13 initiates keratinocyte migration during reepithelialization and osteoclast activation. Fig 1 of Nagase illustrates the structural similarities and differences between known matrix metalloproteases. Further, the degree of % identity of SEQ ID NO 5 to stromelysins does not indicate a particular biological function or activity for SEQ ID NOS 1, 3, or 5, or functional fragments of such, as the art teaches that stromelysins do not necessarily have the same activity. For example, Luo et al (JBC, vol. 277, pp 25527-25536, 2002) teaches that unlike most MMPs, ST3 (MMP 11) is characterized by a distinct substrate specificity and a specific regulation and is not directly involved in extracellular matrix degradation (see abstract). Bodey et al (In Vivo, vol. 15, 2001, abstract) teach that MMP3, and MMP10, corresponding to stromelysins 1 and 2, share 82% sequence homology but

exhibit difference in cellular synthesis and inducibility by cytokines and growth factors in vitro (see abstract). Further, Kerkela et al (British Journal of Cancer, vol. 84, 2001, abstract) teaches that expression of stromelysin 1 (MMP 3) has been shown to correlate with tumor invasiveness in skin tumors, but that stromelysin 2 (MMP 10) expression did not. Therefore, the art does not support a predictable correlation between the structure of stromelysins and their functions. Further, with regard to SEQ ID NO 3 which encodes a protein lacking a key domain that is conserved among MMPs, and SEQ ID NO 1, which encodes only a fragment of a putative MMP, neither the specification nor the art teach a function for such, and therefore, the skilled artisan would be unable to determine whether a nucleic acid sequence belonged to the claimed genus of nucleic acids, other than by SEQ ID NO.

The specification further does not enable a use for the claimed sequences. The specification asserts that nucleic acids of SEQ ID NOS 1, 3, and 5 can be used to express proteins or make probes and primers to detect SEQ ID NOS 1, 3, and 5, however these are non specific uses that would be applicable to any nucleic acid sequence, and does not set forth a specific use for the claimed nucleic acids. The specification further asserts that SEQ ID NOS 1, 3, and 5 could be used to encode proteins wherein inhibition of such would be used to reduce hair growth (see p. 9). The specification cites Styczynski et al (US Patent 5,962,466) as teaching a method of inhibiting hair growth by inhibiting matrix metalloproteases. However, Styczynski et al only teach inhibiting MMP2 and MMP 9 collagenase activity, whereas MMP 2 and MMP 9 only showed 31.6 and 23.2% identity to the protein encoded by SEQ ID NO 5, which is far less than the % identity that the protein encoded by SEQ ID NO 5 exhibited with stromelysins. Given the teachings of

the art as set forth above, that is that matrix metalloproteases, while containing similar domains, have different activities, the skilled artisan would not be able to predictably correlate that inhibition of the polypeptide encoded by SEQ ID NO 5 would result in reducing hair growth based solely on the degree of % identity exhibited by the protein to various other MMPs.

To practice the invention as broadly as it is claimed, the skilled artisan would be required to first determine the substrate specificity and biological activity and function for the polypeptide encoded by SEQ ID NO 5 (SEQ ID NO: 6) and then determine if any of the polypeptides encoded by SEQ ID NOS 1 or 3 possessed the same. The skilled artisan would then be required to mutate every position to determine which amino acids could be changed but still result in a polypeptide with the same function. Additionally claim 3 requires hybridization at unspecified conditions to nucleic acids that encode sequences within SEQ ID NO: 6 wherein hybridization identifies all or a part of an MMP-25 polypeptide. Such recitation encompass a method of detecting any variant, mutant, or homolog nucleic acid sequence of SEQ ID NO: 5, and designating it an "MMP-25" based solely on the fact that it would contain a sequence that would hybridize under unspecified conditions to nucleic acids that encode sequences within SEQ ID NO: 6. However, the specification has provided no predictable correlation that a sequence's ability to hybridize to nucleic acids encoding regions within SEQ ID NO: 6 would render it an "MMP-25" sequence. Further, the specification broadly defines "MMP-25" as including any polypeptide or nucleic acid of the MMP family and having at least 50% up to 95% amino acid identity to SEQ ID NO: 6". It is clear however, that many sequences would be able to hybridize to a nucleic acid encoding regions of SEQ ID NO: 6 that

would not belong in the MMP family let alone be designated an MMP-25. As the specification does not teach the function of SEQ ID NO: 6, the skilled artisan would be required to first determine the activity of SEQ ID NO: 6 (MMP-25) and then would be required to screen each polypeptide encoded by a sequence which was able to hybridize to nucleic acids within SEQ ID NO: 6, to determine which of these sequences was an "MMP-25" polypeptide. As neither the specification nor the art teach a function for the polypeptide encoded by SEQ ID NO 5, let alone that for SEQ ID NOS 1 and 3, the skilled artisan would be required to perform a large amount of trial and error analysis, the results of which are unpredictable given the lack of guidance in the specification and the teachings of unpredictability in the art, to practice the invention as broadly as it is claimed. Such experimentation is considered undue.

Response to Arguments

4. The response traverses the rejection. The response asserts that the specification teaches that SEQ ID NO: 5 encodes a full length MMP-25 polypeptide (SEQ ID NO: 6) that contains conserved motifs known to be present in other matrix metalloproteinases and known to be important for activity of the metalloproteinases. The response further points to specific domains taught by the specification such as zinc binding domains that also bind calcium, and cystein switch motif. This argument has been thoroughly reviewed but was found unpersuasive. As set forth in the previous office action and reiterated above, the examiner has not questioned that SEQ ID NO: 6 most likely belongs in the family of matrix metalloproteases. However, matrix metalloproteases represent a large class of proteins whose members have different functions, such that mere

identification of a protein with this broad class does not make apparent it's function (how one would use the protein) based on the fact that it contains domains that place it in the broad group. For example, Nagase teaches (Nagase and Woessner, J. BC, vol. 274, pp 21491-21494; 1999) that MMPs participate in many normal biological processes such as embryonic development, organ morphogenesis, nerve growth, apoptosis, etc (see p. 21493, col. 1 "Biological and Pathological Roles of Matrixins"). Nagase teaches that while the main function of matrixins is removal of the extracellular matrix during tissue resorption and progression of many diseases, MMPs also alter biological functions of extracellular matrix macromolecules by specific proteolysis. Nagase teaches that MMP-2 cleaves the Ala586-Leu587 bond in laminin and induces the migration of normal breast epithelial cells. In contrast, cleavage of type I collagen by MMP-1 and MMP-13 initiates keratinocyte migration during reepithelialization and osteoclast activation. Fig 1 of Nagase illustrates the structural similarities and differences between known matrix metalloproteases. It should be noted that the specification asserts 1) that SEQ ID NO: 6 has highest homology to the stromelysin family of MMP's and 2) SEQ ID NOS 1, 3, and 5 could be used to encode proteins wherein inhibition of such would be used to reduce hair growth (see p. 9) (The specification cites Styczynski et al (US Patent 5,962,466) as teaching a method of inhibiting hair growth by inhibiting matrix metalloproteases). Such assertions, however, are confusing because it is unclear what specific function for SEQ ID NO 6, the specification is actually asserting. For example, Styczynski et al only teach inhibiting MMP2 and MMP 9 collagenase activity, whereas MMP 2 and MMP 9 only showed 31.6 and 23.2% identity to the protein encoded by SEQ ID NO 5, which is far less than the % identity that the of SEQ ID NO 6 exhibited with stromelysins. Further,

the degree of % identity of SEQ ID NO 5 to stromelysins does not indicate a particular biological function or activity for SEQ ID NOS 1, 3, or 5, or functional fragments of such, as the art teaches that stromelysins do not necessarily have the same activity. For example, Bodey et al (In Vivo, vol. 15, 2001, abstract) teach that MMP3, and MMP10, corresponding to stromelysins 1 and 2, share 82% sequence homology but exhibit difference in cellular synthesis and inducibility by cytokines and growth factors in vitro (see abstract). Further, Kerkela et al (British Journal of Cancer, vol. 84, 2001, abstract) teaches that expression of stromelysin 1 (MMP 3) has been shown to correlate with tumor invasiveness in skin tumors, but that stromelysin 2 (MMP 10) expression did not. The specification's assertion that MMP-25 could be used to inhibit hair growth is based on the fact that certain MMP's are involved in degradation of the extracellular matrix. However, the mechanism for such degradation and substrate specificity is not the same for MMPs in general or even more specifically, with stromelysin's. Luo et al (JBC, vol. 277, pp 25527-25536, 2002) teaches that unlike most MMPs, ST3 (MMP 11) is characterized by a distinct substrate specificity and a specific regulation and is not directly involved in extracellular matrix degradation (see abstract). Therefore as illustrated by the teachings in the art, there is no predictable correlation as to the function and specificity of a particular polypeptide based on domain/homology analysis to known MMPs or more particularly, the class of stromelysins.

The response asserts that the instant specification also enables a person skilled in the art to make and use a nucleic acid molecule that is at least 85% identical to the nucleotide sequence set forth in SEQ ID NO: 5 as the claims recite "wherein the nucleic acid molecule encodes a MMP-25 polypeptide that exhibits the same catalytic activity

that is the same as that of a wild-type MMP-25 polypeptide comprising the amino acid sequence of SEQ ID NO: 6". The response asserts that the instant specification teaches that MMP-25 variants include polynucleotides that encode polypeptides that retain the structural and functional characteristics of an MMP-25 polypeptide that the variants can be identified and functionally characterized by alignment methods, by the ability to bind specifically an anti-MMP 25 antibody and/or by the ability to degrade the same panel of protein substrates with the same relative catalytic activity as wild type MMP-25. This argument has been thoroughly reviewed but was not found persuasive. Firstly, it is noted that neither the specification nor the art teach a specific anti-MMP 25 antibody or the protein substrate that MMP-25 degrades. As such the specification also does not teach the catalytic activity of MMP-25 such that the skilled artisan would be able to determine a protein that had a catalytic activity "relative" to that of MMP25. Such examples represent an invitation for further experimentation, they do not teach how to make or use a specific molecule but rather teach methods for looking for operative embodiments that are within the scope of the instant claims. This is not the same as a specific teaching of how to make or use the claimed nucleic acids.

Additionally, the art does not support the response's assertion that alignment methods such as BLAST can predictably establish the function or biological activity of an unknown protein. For example, Fetrow teaches (Fetrow et al., J. Mol. Biol., vol. 282, pp 703-711, 1998) that although function prediction by homology to previously characterized proteins is extremely successful and is fast, cheap and reliable, there are several problems that limit its potential utility, one of which is that sequence homology does not guarantee functional similarity (p 704, col. 1, 1st full paragraph). Fetrow

teaches that "threading"(analysis using structure prediction tools) can identify topological cousins, that is, protein families such as the α/β barrels with similar structures, but dissimilar functions. Fetrow teaches using a three dimensional descriptor of the active site of a protein, termed "fuzzy functional form" (FFF) and argues that threading alone is not enough to provide the required information about function because it has been shown that pairs of proteins can have similar structures but unrelated functions (p. 706, col. 2, last para). Fetrow teaches that because such topological cousins exist, knowledge of the structure is not equivalent to identification of protein function. Skolnick (Skolnick and Fetrow, TIBTECH, January 2000, vol. 18, pp 34-39) teaches (p. 35, "Box 1") that a common protein characteristic that makes functional analysis based only on homology especially difficult is the tendency of proteins to be multifunctional. Skolnick teaches that for example, lactate dehydrogenase binds NAD, substrate, and zinc and performs a redox reaction and that each of these occurs at different functional sites that are in close proximity and the combination of all four sites creates the fully functional proteins. Skolnick also cites RecA which contains a DNA binding domain, a multimerization domain and additional sites that bind regulatory proteins. Skolnick also teaches that the serine threonine phosphatase superfamily is a prime example of the difficulties of using standard sequence analysis to recognize the multiple functions found in single proteins. Skolnick teaches that this large protein family is divided into a number of subfamilies, all of which contain an essential phosphatase active site. He teaches that subfamilies 1, 2A and 2b exhibit 40% or more sequence identity between them, however each of these subfamilies is apparently regulated differently by the cell and observation suggest that there are different functional sites at which regulation can occur. Skolnick teaches that

because the sequence identity between subfamilies is so high, standard sequence similarity methods could easily misclassify new sequences as members of the wrong subfamily if the functional sites are not carefully considered. Therefore, although the alignment studies provided by the specification indicate that the claimed polypeptide contains zinc binding domains a hemopexin domain and a cystein switch domain, and that the claimed polypeptide likely belongs to the matrix metalloprotease family, such alignment is not sufficient to indicate to the skilled artisan the specific function or biological activity of the claimed polypeptides, so that the artisan would know how to use the claimed invention. The art with regard to sequence homology specifically teaches that sequence alignment alone does not necessarily provide a predictable correlation between the structure and specific function of a protein. The art with regard to matrix metalloproteases, as cited above, demonstrates that alignment methods with SEQ ID NO: 6 provide a variety of different proteins that have different biological functions and specificities, any of which SEQ ID NO: 6 may share. The specification, however, has not taught the actual activity or specificity of SEQ ID NO: 6, therefore it is unclear which of these functions and specificities SEQ ID NO: 6 would be predictably associated with. While one of skill in the art could determine the activity of SEQ ID NO: 6, the teachings of the specification do not provide the skilled artisan with a predictable correlation as to what that particular activity or substrate specificity is. As asserted in the response, MMPs degrade a number of different proteins such as collagens, laminins, gelatins, aggrecans, fibronectins, etc, however as illustrated by the cited art, different MMPs exhibit different substrate specificities. They do not all degrade the laundry list of proteins provided in the response. The proteolytic assay for determining activity

referenced in the response represents further experimentation that must be conducted to actually determine the activity of SEQ ID NO: 6 and to determine which nucleic acid molecules would be encompassed by the scope of the claims. As stated earlier, such experimentation represents a method of looking for operative embodiments, which is not the same as a teaching of what those operative embodiments actually are. Given that the art indicates that the function of MMP25 (SEQ ID NO: 6) is not predictable based on the possession of certain domains and homology to a large class of proteins with different functions, the assertion in the response that such experimentation is "merely a matter of routine screening" is not found persuasive.

The response further asserts that the specification enables a use for the claimed nucleic acids and teaches for example, that MMP expression in a cell may affect one or more physiological process such as angiogenesis, photoaging of skin, cancer, and hair growth. This argument has been thoroughly reviewed but was not found persuasive as these processes are very different, having different modes of action, and involve different proteins. It is unclear which of these general processes MMP-25 is associated with, or how it MMP 25 would function in such a diverse list of possible physiological processes. The specification does not teach such, but instead leaves it up to the skilled artisan to determine which general process, which specific mechanism within a general process, how, and with what type of specificity SEQ ID NO: 6 functions. The response asserts that unlike the lack of teachings of Styczynski, the instant specification teaches that the claimed nucleic acid molecules encoding a MMP-25 polypeptide are preferentially expressed in the inner root sheath layer of hair follicle, particular in the Henle layer which contains cells involved in hair growth. This argument was thoroughly reviewed

but was found unpersuasive. The specification teaches that SEQ ID NOS 3 and 5 were expressed in fetal skin and in mammary glands (page 63). This expression analysis, however, does not make readily apparent or predictably associate the specific function, specific biological activity, or substrate specificity of SEQ ID NOS: 3 and 5 vs other MMPs or other stromelysins.

The responses' assertion that using nucleic acids molecules of SEQ ID NOS 1, 3, and 5 to express proteins or to make probes and primers to detect these polynucleotides are specific uses is not found persuasive because absent knowledge of how to use the specific polypeptides of SEQ ID NOS 4 and 6, the use of a nucleic acid to encode a protein or to make probes or primers to detect itself are characteristic of any nucleic acid sequence and not specific to MMP-25. For these reasons and the reasons made of record in the previous office action and reiterated above, the rejection is maintained.

Written Description

5. Claims 1, 5-7 and 26-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to nucleic acids that comprise "a nucleotide sequence as set forth in SEQ ID NOS 3, and 5", nucleic acid sequence encoding a polypeptide "comprising an amino acid sequence as set forth in SEQ ID NOS 4 and 6". Such recitation encompasses sequences that can comprise any fragment from within SEQ

ID NO: 3 and 5, and includes a vary large genus of mutants, variants, and homologs of SEQ ID NOS 3 and 5, from any source, as well as unrelated sequences, including genomic sequences. The claims are further drawn to nucleic acid sequences that are at least 85% identical to the nucleotide sequence of the nucleotide sequence set forth in SEQ ID NO 5 wherein the nucleic acid molecule encodes an MMP-25 polypeptide that exhibits catalytic activity that is the same as that of a wild-type MMP-25 polypeptide comprising the amino acid sequence of SEQ ID NO: 6, and nucleic acid molecules that encode MMP-25 polypeptide variants which comprise an amino acid sequence at least 90 or 95% identical to the sequence set forth in SEQ ID NO: 6, and wherein the variant exhibits the same catalytic activity of the polypeptide of SEQ ID NO: 6. As the specification does not teach or describe the activity of SEQ ID NO: 6, the claims encompass unknown functional variants and homologs of SEQ ID NO 6, from any source, that have neither been taught or described by the specification.

The specification teaches that SEQ ID NO 5 encodes a matrix metalloprotease that has the highest % identity to the stromelysin family of matrix metalloproteases (46%). The specification teaches that SEQ ID NO 3 encodes a splice variant of SEQ ID NO 5,which lacks a Zn binding domain. The specification teaches that SEQ ID NO 1 encodes a fragment of SEQ ID NO 5, and SEQ ID NO 3. The specification teaches that the claims encompass variants that retain structural and functional characteristics more similar to MMP 25 (polypeptide encoded by SEQ ID NO 5) than to non type MMP 25 polypeptides. However, the specification does not teach the specific biological activity or function of SEQ ID NOS 3 or 5, such that the skilled artisan could determine whether a nucleic acid encoded a polypeptide belonging to such a large genus of polypeptides based

solely on possession of a few nucleic acids in common with SEQ ID NO: 3 or 5, or based on having a certain percent amino acid sequence or nucleic acid sequence identity with SEQ ID NOS 6 or 5, respectively. The disclosure of the sequence of SEQ ID NOS 1, a fragment, 3, a splice variant, and 5, a full length nucleic acid sequence, is not representative of the large genus of mutants, functional variants and homologs of SEQ ID NO: 6, from any source.

While SEQ ID NO 5 appears to belong to the family of Matrix Metalloproteases, Matrix Metalloproteases comprise a large group of proteins that are involved in the degradation of the extracellular matrix (see Yang and Kurkinen, J. BC, 1998; vol. 273, p 17893, col 1). This large group of proteins share similar domains with distinct structure and function, and have wide and often overlapping substrate specificities depending on the group they are in. These groups include collagenases, gelatinases, stromelysins, and membrane-type MMPs. However, this large group of proteins have different biological functions. Nagase teaches (Nagase and Woessner, J. BC, vol. 274, pp 21491-21494; 1999) that MMPs participate in many normal biological processes such as embryonic development, organ morphogenesis, nerve growth, apoptosis, etc (see p. 21493, col. 1 "Biological and Pathological Roles of Matrixins"). Nagase teaches that while the main function of matrixins is removal of the extracellular matrix during tissue resorption and progression of many diseases, MMPs also alter biological functions of extracellular matrix macromolecules by specific proteolysis. Nagase teaches that MMP-2 cleaves the Ala586-Leu587 bond in laminin and induces the migration of normal breast epithelial cells. In contrast, cleavage of type I collagen by MMP-1 and MMP-13 initiates keratinocyte migration during reepithelialization and osteoclast activation. Fig 1 of

Nagase illustrates the structural similarities and differences between known matrix metalloproteases. Further, the degree of % identity of SEQ ID NO 5 to stromelysins does not indicate a particular biological function or activity for SEQ ID NOS 1, 3, or 5, or functional fragments of such, as the art teaches that stromelysins do not necessarily have the same activity. For example, Luo et al (JBC, vol. 277, pp 25527-25536, 2002) teaches that unlike most MMPs, ST3 (MMP 11) is characterized by a distinct substrate specificity and a specific regulation and is not directly involved in extracellular matrix degradation (see abstract). Bodey et al (In Vivo, vol. 15, 2001, abstract) teach that MMP3, and MMP10, corresponding to stromelysins 1 and 2, share 82% sequence homology but exhibit difference in cellular synthesis and inducibility by cytokines and growth factors in vitro (see abstract). Further, Kerkela et al (British Journal of Cancer, vol. 84, 2001, abstract) teaches that while expression of stromelysin 1 (MMP 3) has been shown to correlate with tumor invasiveness in skin tumors, but that stromelysin 2 (MMP 10) expression did not. Therefore, the art does not support a predictable correlation between the structure of stromelysins and their functions. Further, with regard to SEQ ID NO 3 which encodes a protein lacking a key domain that is conserved among MMPs, and SEQ ID NO 1, which encodes only a fragment of a putative MMP, neither the specification nor the art teach a function for such, and therefore, the skilled artisan would be unable to determine whether a nucleic acid sequence belonged to the claimed genus of nucleic acids, other than by SEQ ID NO.

The claims encompass an extremely large genus of nucleic acids, such that the recitation of SEQ ID NO 3 or 5, or the partial fragment of SEQ ID NO 1 does not provide a teaching of a substantial portion of the claimed genus of mutants, variants, or

homologs, or genomic sequences corresponding to such, from any source. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NOS: 1, 3, and 5, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

It is noted that as the nucleic acid sequences of claims 1, and 26-31 lack sufficient written description, claims drawn to complementary sequences, and vectors and host cells comprising such sequences also lack sufficient written description.

Response to Arguments

6. It is noted that the amendment has overcome the rejection with regard to claims 3 and 4.

7. The response traverses the rejection. The response asserts that the specification provides sufficient relevant identifying characteristics of the claimed nucleic acid molecules. The response asserts that the specification teaches that MMP 25 is a new member of the matrix metalloprotease family, the specification describes the sequence of SEQ ID NO: 5 and the subsequent encoded polypeptide (SEQ ID NO 6) which contains conserved motifs with MMPs. This argument was thoroughly reviewed but was not found persuasive. As set forth in the previous office action and reiterated above, the family of MMPs is a large class of proteins whose members have different, and in certain cases, distinct biological activities and substrate specificities. Membership to this broad class of endopeptidases does not make apparent the specific function or substrate specificity of SEQ ID NO: 6 (MMP-25). Further, as the specification does not teach the function or specificity of SEQ ID NO: 6 or which amino acids could be modified but still

maintain such unknown activity and specificity, the specification has not described a substantial portion of the mutants, functional variants, and homologs encompassed by the claims. The recitation's assertion that relevant identifying characteristics include "a nucleic acid molecule that is at least 85% identical to SEQ ID NO: 5 but encodes a protein with the same catalytic activity of SEQ ID NO: 6" because such variants preferably contain conservative amino acid substitutions that such that the variants retain structural and functional characteristics of wild-type MMP 25 was not found persuasive because the specification has not in fact described the activity of wild type MMP-25. The specification provides general methods that the skilled artisan could carry out to determine such activity, however this is not the same as a description of the activity itself. In first determining the activity of SEQ ID NO: 6, and then mutating every position or even certain positions to determine amino acids could tolerate substitutions, even conservative substitutions, represents a method of determining embodiments that fit within the scope of the claims. This is not the same as describing the actual variants that are encompassed by the claims. As noted by the courts, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a

potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

The response further asserts that an MMP 25 variant can be structurally characterized by its amino acid sequence, such as conserved motifs, and functionally characterized by its ability to bind to antibodies that are specific for wildtype MMP 25 or by proteolytic activity (in that most MMPs have overlapping substrate specificity). This argument has been thoroughly reviewed but was not found persuasive. As stated in the last office action and reiterated above, MMPs are large class of proteins that have different functions and substrate specificities. They do not all degrade the full laundry list of substrates provided in the response, therefore, while they function as endopeptidases, it is not immediately apparent from the fact that they share motifs common to MMPs, as to which substrates they degrade. Further, the response mentions antibodies that are specific to wild type MMP-25, however, the specification has not taught or described such an antibody. Therefore to use such an antibody to obtain operative embodiments from within the broad scope of the claims, the skilled artisan would first have to obtain this antibody. Again, such teaching represents a method of determining which embodiments are operable, which is not the same as describing the structure of the functional variants themselves.

The response further asserts that the specification describes relevant identifying characteristics of a splice variant of MMP-25, (SEQ ID NO: 4) which is a polypeptide characterized by a 43 amino acid deletion comprising the zinc/calcium binding domain. This argument was thoroughly reviewed but was found unpersuasive because it is unclear what structure function correlation can be made with regard to SEQ ID NO: 4 and 6 when

the function of neither protein is taught or demonstrated by the specification. It is clear that SEQ ID NO: 4 does not represent "relevant identifying characteristics" of functional variants because lack of the zinc/calcium binding domain, a domain relied upon by the specification with regard to MMP-25 activity, would not represent a variant with the same function as wild type MMP-25. (In other words, how can a protein that relies upon a specific domain for an activity be expected to have the same activity as another protein, identical except that it is missing this critical domain?) Further, because the specification does not teach the function of either SEQ ID NO: 4 or SEQ ID NO: 6, the disclosure of SEQ ID NO: 4 does not represent "relevant identifying characteristics" of non functional variants because the specification has not established a correlation between the altered structure of this splice variant and any difference in function from wild type MMP-25. Therefore, it is unclear what "relevant identifying characteristics" are made apparent by the disclosure of SEQ ID NO: 4. While it may represent a non functional variant, it's unclear which "function" is altered, or whether any function is altered, as the specification has not demonstrated its activity. The same reasoning can be applied to the disclosure of the fragment of SEQ ID NO:1 (again, no structure/function correlation has been described for SEQ ID NO: 1). For these reasons, and the reasons made of record in the previous office action, the rejection is maintained.

Claim Rejections - 35 USC § 102

8. The rejection of claim 1 under 35 USC 102(e) as being anticipated by Robison and the rejection of claims 3-7 under 35 USC 103(a) as being obvious in view of Robison

are moot in view of the declaration submitted under 37 CFR 1.131. The declaration filed on 11/12/2003 under 37 CFR 1.131 is sufficient to overcome the reference.

9. Claims 26 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Accession number AA424347 (Oct. 1997).

Accession number AA424347 teaches a sequence which is identical to positions 653-1063 of SEQ ID NO 3, and positions 741-1151 of SEQ ID NO 5, therefore the accession number teaches a nucleic acid molecule that comprises "a" nucleotide sequence as set forth in" SEQ ID NO: 3 and SEQ ID NO: 5. The claims are not limited to sequences that comprise the [full length] sequence of SEQ ID NOS 3 or 5. Further, the sequence of the complete complement of Accession number AA424347 is inherently set forth in the teachings of the sequence, wherein the complement meets the limitations of the claims.

Response to Arguments

10. The response traverses the rejection. The response asserts that the cited reference fails to teach or suggest an isolated nucleic molecule that comprises a nucleotide sequence set forth in SEQ ID NO: 3 or 5. This argument was not found persuasive. As stated above, the accession number teaches an isolated nucleic acid molecule that comprises *a* sequence set forth in SEQ ID NOS 3 and 5 (it comprises a sequence such as positions 653-1063 of SEQ ID NO: 3 and 741-1151 of SEQ ID NO: 5). It is noted that the rejection can be overcome by reciting instead "... comprising --the-- [a] nucleotide sequence of SEQ ID NO: 3..." (or SEQ ID NO: 5, respectively).

11. Claims 25-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US Patent 5,474,796).

Brennan teaches making an array of all possible isolated trimer nucleic acid sequences (see Fig. 1). The recitation of "a nucleotide sequence..." encompasses fragment sequences within the cited SEQ ID NOS, which are taught by Brennan.

12. Claims 26, 27, and 5-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Yang and Kurkinen (J. BC, 1998; vol. 273, pages 17893-17990).

Yang and Kurkinen teach a sequence which comprise *a* sequence set forth in SEQ ID NO 3 and SEQ ID NO: 5 (Fig 1). The sequence of Yang and Kurkinen is identical at positions 183-187 to positions 170-174 of SEQ ID NO 3 and positions 129-133 of SEQ ID NO 5. The claims are not limited to sequences that comprise the [full length] sequence of SEQ ID NOS 3 or 5. Yang and Kurkinen further teach vectors and host cells comprising such sequence (page 17894, col 2 "cDNA Cloning and sequence analysis).

Conclusion

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

14. No claims are allowable.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0572. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

Note: The examiner's name has changed from Jehanne Souaya to Jehanne Sitton. All future correspondence to the examiner should reflect the change in name.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272-0745. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (571) 272-0507.

Jehanne Sitton

Jehanne (Souaya) Sitton
Primary Examiner
Art Unit 1634

2/5/04